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(71) Applicant *(for all designated States except US)*:
NEURO3D [FR/FR]; 12, allée Nathan Katz, F-68100 Mulhouse (FR). **UNIVERSITE LOUIS PASTEUR** [FR/FR]; 4, rue Blaise Pascal, F-67000 Strasbourg (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*:
BOURGUIGNON, Jean-Jacques [FR/FR]; 14, rue de Bruhly, F-67150 Hipsheim (FR). **LAGOUGE, Yan** [FR/FR]; 16, cite Spach, F-67000 Strasbourg (FR). **LUGNIER, Clair** [FR/FR]; 37, rue d'Ypres, F-67000 Strasbourg (FR).

(74) Agents: **TEZIER HERMAN, Béatrice;** Becker et Associates, 35, rue des Mathurins, F-75008 Paris (FR).

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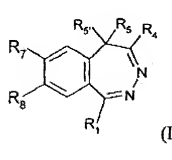
(54) **Title:** COMPOUNDS INHIBITING CYCLIC NUCLEOTIDE PHOSPHODIESTERASES, PREPARATION AND USES THEREOF

(57) **Abstract:** The invention relates to novel 2,3-benzodiazepine derivatives and uses of the same in the field of therapy. The invention also concerns methods for preparing the same and novel synthesis intermediates. The compounds of the invention correspond more particularly to General Formula (I) or (I').



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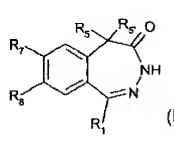


(I')

Cyclic nucleotide phosphodiesterases inhibiting compounds, preparation and uses

The invention relates novel derivatives of the 2,3-benzodiazepine type and applications for the same in field of therapy. It also relates processes for preparation of the same and novel synthesis intermediates.

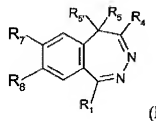
The compounds for which synthesis is described in the present invention are novel and have highly advantageous pharmacological properties: they inhibit cyclic nucleotide phosphodiesterases and particularly Type IV AMPc-phosphodiesterase (PDE4), and thus have highly advantageous therapeutic applications.

The functions of the most tissues are modulated by endogenous substances (hormones, transmitters, etc) or exogenous substances. The biological effects of some of these substances are transmitted at the intracellular level by enzymatic effectors, such as adenylate cyclase or guanylate cyclase. Stimulation of these enzymes results in an increase in levels of intracellular cyclic AMP (AMPc) or cyclic GMP (GMPc), which are second messengers involved in the regulation of many cellular activities. These cyclic nucleotides are degraded by a family of enzymes, the phosphodiesterases (PDEs), which are divided into at least 7 groups. One of these is PDE4, which is present in many tissues (heart, brain, vascular or tracheo-bronchial smooth muscle, etc.) and specifically hydrolizes cyclic AMP.

By slowing down the degradation of cyclic AMP, PDE4 inhibiters increase or maintain AMPc levels in cells, and are notably used in the treatment of inflammatory diseases or tracheo-bronchial smooth musculature pathologies, by combining an anti-inflammatory effect with smooth muscle relaxation.

The applicant has now demonstrated that certain 2,3-benzodiazepines or benzodiazepin-4-ones are effective as cyclic nucleotide phosphodiesterases inhibitors, and in particular PDE4 inhibiters. The invention also describes novel compounds having a potent PDE4 inhibiting activity, and preferably having an excellent selectivity profile with regard to the other PDE isomers, and in particular having a weak action on PDE3. Moreover, the preferred compounds according to the invention have anti-iinflammatory properties and/or significant central [nervous system] effects (anticonvulsive, anxiolytic, sedative, antidepressant), and are advantageously free of hypotensive or emetic effects.

More particularly, the invention has as its object compounds represented by general formula (I) or (I')



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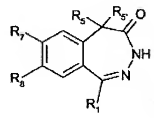


(I')

wherein:

- R_1 is a (C_1-C_8) alkyl group, (C_3-C_6) cycloalkyl group, (C_6-C_{18}) aryl group, (C_6-C_{18})aryl(C_1-C_4)alkyl group, (C_1-C_6)alkyl(C_6-C_{18})aryl group, or (C_5-C_{18}) heteroaryl group having 1 to 3 heteroatoms, or a OR_2, SR_2 or NR_2R_3 group wherein: (i) R_2 and R_3,

independently of each other, are chosen from a hydrogen atom, a (C_1-C_6) alkyl group, (C_3-C_6)cycloalkyl(C_6-C_{12})aryl group, or (C_5C_{12}) heteroaryl group having 1 to 3 heteroatoms; or (ii) R_2 and R_3 together form a straight or branched hydrocarbon chain having 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally being interrupted by a nitrogen, sulfur or oxygen atom;

- R_4 is a halogen atom or a (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2C_6) alkynyl or phenyl group or an OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined above;

- R_5 and R_5', independently of each other, are chosen from a hydrogen atom, a (C_1-C_6) alkyl group, a phenyl group, substitued phenyl group or substituted or unsubstituted (C_1-C_6) alkylphényl group or, R_5 and R_5' together form a straight or branched hydrocarbon chain having 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally interrupted by an oxygen sulfur or nitrogen atom;

- R_7 and R_8, independently one of the other, are selected from a hydrogen atom and an OR_2, R_2 group being as defined above,

the alkyl, cycloalkyl, aryl, heteroaryl, alkenyl and alkynyl groups and the hydrocarbon chain defined above optionally being substituted by one or more substituents, which may be the same or different, and are preferably selected from a halogen atom, an OH, =O, NO_2, NH_2, CN, COOH, or CF_3 group, a (C_1-C_6) alkoxy group or an $NHCOR_2$ or $CONR_2R_3$ group, wherein and R_2 and R_3 are as defined above,

for the preparation of a pharmaceutical composition intended for the inhibition of a cyclic nucleotide phosphodiesterase, and in particular phosphodiesterase 4 (PDE4). More specifically, the invention relates to the use of the foregoing compounds for the treatment of pathologies involving deregulation of intracellular cyclic AMP levels.

The invention is also directed to novel compounds according to General Formula (I) or (I') such as defined below.

The invention also relates to pharmaceutical compositions comprising one or more compounds such as defined above and a pharmaceutically acceptable vehicle or an excipient.

According to the invention, the term "alkyl" indicates a straight or branched hydrocarbon radical advantageously having from 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, neopentyl, or n-hexyl. C_1-C_4 groups are preferred. The alkyl groups may be substituted by an aryl group such as defined hereinafter, in which case it is referred to as an arylalkyl group. Examples of arylalkyl groups are, in particular, benzyl and phenethyl.

The term "cycloalkyl" indicates a cyclic hydrocarbon system, which may advantageously comprise 3 to 6 carbon atoms and be mono- or poly-cyclic. Particular examples include cyclopropyl and cyclohexyl groups. "Aryl" groups are mono-, bi- or tri-cyclic aromatic hydrocarbon systems, and preferably monocyclic or bicyclic aromatic hydrocarbons comprising from 6 to 18 carbon atoms, and more preferably 6 carbon atoms. Examples include phenyl, naphthyl and biphenyl groups.

"Heteroaryl" groups indicate hydrocarbon systems, which may or may not be aromatic, comprising one or more cyclic heteroatoms. These are preferably cyclic aromatic hydrocarbon systems comprising from 5 to 18 carbon atoms and one or more

cyclic heteroatoms, and in particular from 1 to 4 cyclic heteroatoms chosen from N, O or S. Preferred heteroaryls include in particular benzothienyl, benzofuryl, pyrrolidinyl, morpholino, thiazolyl, thienyl, furyl, pyranyl, pyrrolyl,2H-pyrrolyl, imidazolyl, benzymidazolyl, pyrazolyl, isothiazolyl, isoxazolyl et indolyl groups.

The aryl and heteroaryl groups can be substituted by an alkyl, alkenyl or alkynyl group such as defined above. In this case, an aryl or a heteroaryl substituted by an alkyl group is called an alkylaryl. Particular examples of alkylaryl groups are tolyl, methyl and xylyl. In this case, an aryl or a heteroaryl substituted by an alkenyl group is called an alkenylaryl. Particular examples of alkenylaryl groups are cinnamyl groups. In this case, an aryl or a heteroaryl substituted by an alkynyl is called an alkynylaryl group.

"Alkenyl" groups are straight or branched hydrocarbon radicals comprising one or more double bonds. They advantageously comprise from 2 to 6 carbon atoms and, preferably, 1 or 2 double bonds. The alkenyl groups can be substituted by an aryl group such as defined above, in which case this is called a arylalkenyl group.

"Alkynyl" groups are straight or branched hydrocarbon radicals comprising one or more triple-bonds. They advantageously comprise from 2 to 6 carbon atoms and, preferably, 1 or 2 double bonds. The alkynyl groups can be substituted by an aryl group such as defined above, in which case this is called an arylalkynyl group.

"Alkoxy" groups correspond to the alkyl and cycloalkyl groups defined above linked to the nucleus by way of an -O- (ether) bond. Methoxy and ethoxy groups are especially preferred.

"Halogen" means an iodine, bromine, chlorine or fluorine atom.

"Heteroatom" means an atom chosen from O, N and S.

More particularly, the invention is directed to compounds of General Formula (I) or (I') such as defined above in which R_4, R_5, R_5', R_7 and R_8 are as defined above and R_1 is a (C_1-C_6) alkyl group, (C_3-C_6) cycloalkyl group, (C_1-C_6)alkyl(C_6-C_{18})aryl group or (C_5-C_{18}) heteroaryl group comprising 1 to 3 heteroatoms, or an OR_2, SR_2 or NR_2R_3 group wherein: (i) R_2 et R_3, independently of each other, are chosen from a (C_1-C_8) alkyl group, a (C_3-C_6)cycloalkyl(C_6-C_{12})aryl group, or a (C_3-C_{12}) heteroaryl group having 1 to 3 heteroatoms; or (ii) R_2 et R_3 together form a straight or branched hydrocarbon chain of 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally being interrupted by a nitrogen, sulfur or oxygen atom.

Thus, the invention is more particularly directed to compounds of General Formula (I) or (I') such as defined above, in which R_1, R_4, R_5, R_5', R_7 and R_8 are such as defined above, excluding compounds wherein:

- R_1 represents the group 3,4-dimethoxyphenyl, R_4 represents methyl, R_5 represents ethyl, R_5' represents hydrogen and R_7 and R_8 represent methoxy;
- R_1 represents the group 4-aminophenyl, R_4 represents methyl, R_5 and R_5' represent hydrogen and R_7 and R_8 represent methoxy;
- R_1 represents the group 3-chlorophenyl, R_4 represents methyl, R_5 and R_5' represent hydrogen and R_7 and R_8 represent methoxy

The invention is also directed to compounds of General Formula (I) or (I') such as defined above, excluding compounds of Formula (I) wherein R_5 represents a substituted (C_1-C_6) alkyl or phenyl radical and R_5 represents a hydrogen atom, and excluding compounds according to Formula (I) wherein R_5 and R_5' simultaneously represent a hydrogen atom, in particular wherein R_7 and R_8 represent a methoxy group and R_1 represents a diethoxyphenyl group or 3-chlorophenyl.

The invention is also directed to compounds according to General Formula (I) wherein R_1, R_4, R_5, R_5', R_7 and R_8 are as defined above, provided R_4 does not represent methyl.

The invention is also directed to compounds of General Formula (I) wherein R_1, R_5, R_5', R_7 and R_8 are as defined above and R4 is an halogen atom a (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or phenyl group or an OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined above.

The invention is moreover directed to compounds according to General Formula (I) or (I') wherein R_4, R_5, R_5', R_7 and R_8 are as defined above and R_1 is: (i) a (C_1-C_6) alkyl group, (C_3-C_6) cycloalkyl group or (C_5-C_{12}) heteroaryl group comprising 1 to 3 heteroatoms; or (ii) an OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined above.

Preferred are compounds of General Formula (I) above wherein R_4 is selected from an halogen atom and preferably chlorine, a (C_2-C_6) alkynyl group, and a NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom, a (C_1-C_6) alkyl or (C_1-C_6) hydroxyalkyl group; or (ii) R_2 and R_3 together form a chain with the formula $-(CH_2)_m(O)_n-(CH_2)_2-$ wherein m is an integer from 2 to 3 and n is equal to 0 or 1.

In a particular mode of embodiment of the invention, R_4 represents the NR_2R_3 group wherein: (i) R_2 represents a hydrogen atom and R_3 is selected from a (C_1-C_6) alkyl group and a (C_1-C_6) hydroxyalkyl group; or (ii) R_2 and R_3 together form a chain with the formula $-(CH_2)_m(O)_n-(CH_2)_2-$, wherein m is an integer from 2 to 3, preferably equal to 2, and n is equal to 0 or 1. A particular group comprises compounds wherein R_4 represents the NR_2R_3 group, R_2 and R_3 each representing a (C_1-C_6) alkyl group.

In a particular mode of embodiment of the invention, the compounds of Formula (I') are as defined above and R_1 is a substituted phenyl group or an optionally substituted naphtyl group.

According to another mode of embodiment of the invention, the compounds of General Formula (I) or (I') are as defined above and R_1 is a (C_6-C_{18}) aryl group, and preferably an unsubstituted phenyl group.

Another preferred group includes the compounds of General Formula (I) or (I') as defined above, wherein R_1 is a heteroaryl group, which may or may not be substituted. Such compounds present a particularly marked phosphodiesterase inhibiting action.

Another particularly preferred group is constituted by the compounds of General Formula (I) or (I') as defined above, wherein R_7 and R_8 represent an ethoxy group, with the exception of the compound 1-(2-chlorophényl)-4-methyl-7,8-diethoxy-5*H* 2,3-benzodiazepine. As shown in the examples, such compounds present a particularly marked phosphodiesterase inhibiting action.

Within this framework, the preferred compounds of Formula (I) are those for which of Formula (I) [*sic*] wherein R_4 and R_5 represent a hydrogen atom or a (C_1-C_6) alkyl radical, R_4 and R_5 not simultaneously being an hydrogen atom, and R_5 advantageously representing a (C_1-C_6) alkyl radical.

Particular compounds are the compounds of General Formula (I) wherein R_1 is an unsubstituted phenyl group, R_4 is a halogen, a (C_2-C_6) alkyl group or a (C_2-C_6) alkynyl group, or an NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom or a (C_1-C_6) alkyl group; or (ii) R_2 and R_3 together form a $(CH_2)_n$ group, n being a whole number between 3 and 6 inclusively, or a $(CH_2)_2O(CH_2)_2$ group, R_5 and R_5' are [each] a hydrogen atom and R_7 and R_8 [each] represent an OMe group.

Other particularly advantageous compounds are compounds of General Formula (I) or (I') wherein R_1 is a heteroaryl group, R_7 and R_8 [each] represent an ethoxy group, and R_4, R_5 and R'$_5$ [*sic*] are as defined above. Preferably, R_4 is a (C_1-C_3) alkyl group, R_5 is a hydrogen atom or a (C_1-C_3) alkyl group, and R_5' is a hydrogen atom.

In general, the compounds of Formula (I) or (I') presenting the best activities are those wherein:

- R_1 is a substituted phenyl group (in particular 4-chlorophenyl, fluorophenyl, bromophenyl, hydroxyphenyl or methoxyphenyl), 2-benzo[b]thienyl, 4-(2-furyl)phenyl, 2-naphtyl, 4-biphenyl, cinnamyl, and/or
- R_4 is a (C_1-C_6) alkyl or (C_2-C_6) alkynyl group, or a SH or OH group, in particular (C_1-C_3) alkyl group, and especially methyl or ethyl; and/or
- R_5 and R_5' are [each] a hydrogen atom and/or
- R_5 is a (C_1-C_3) alkyl group, in particular ethyl or propyl, and R_5' is a hydrogen atom, and/or
- R_7 and R_8 [each] represent a methoxy or ethoxy group, and preferably an ethoxy group.

Particularly preferred compounds are as follows:

-Tofisopam, Girisopam, Nerisopam,

-7,8-dimethoxy-1-(2-naphthyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(4-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-7,8-dimethoxy-1-[(4-phenyl)phenyl]-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(5-chloro-2-naphtyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(3-chlorophenyl)-7,8-diethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(benzo[b]thienyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4one,

-7,8-dimethoxy-1-[(3-phenyl)phenyl]-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(benzo[b]thienyl)-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine,

-1- (benzo[b]thienyl)-7,8-diethoxy-4-methyl-5*H*-2,3-benzodiazepine,

-1-(2-benzo[b]thienyl)-7,8-diethoxy-5-n-propyl-3,5-dihydro-4*H*-2,3benzodiazepin-4-one,

-1-(cinnamyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-7,8-diethoxy-5-ethyl-1-(2-fluorophenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4one,

-1-(2-chlorophenyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-7,8-diethoxy-5-ethyl-1-(2-hydroxyphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-7,8-diethoxy-5-ethyl-1-(2-methoxyphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

-1-(2-benzo[b]thienyl)-7,8-diethoxy-4-methyl-5-*n*-propyl-5*H*-2,3-benzodiazepine,-1-(cinnamyl)

-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine

-7,8-diethoxy-5-ethyl-1-(2-fluorophenyl)-4-methyl-5*H*-2,3-benzodiazepine

-1-(2-chlorophenyl)-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine

-7,8-diethoxy-5-ethyl-1-(2-hydroxyphenyl)-4-methyl-5*H*-2,3-benzodiazepine

-7,8-diethoxy-5-ethyl-1-(2-methoxyphenyl)-4-methyl-5*H*-2,3-benzodiazepine

Others specific compounds according to the invention are the following:

7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,

1-(3-chlorophenyl)-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine,

7,8-dimethoxy-4-methylamino-1-phenyl-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-1-phenyl-4-(pyrrolidin-1-yl)-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-4-(*N,N*-dimethylamino)-1-phenyl-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-1-phenyl-4-N-propylamino-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-4-(1-morpholino)-1-phenyl-5*H*-2,3-benzodiazepine,
4-(2-hydroxyethylamino)-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine,
4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-1-phenyl-4-(prop-1-ynyl)-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-1-phenyl-4-N-propyl-5*H*-2,3-benzodiazepine,
4-*n*-butyl-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine,
4-mercapto-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine,
7,8-dimethoxy-5-methyl-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
4,7,8-trimethoxy-1-phenyl-5*H*-2,3-benzodiazepine,
1-benzyl-3,5-dihydro-7,8-dimethoxy-4*H*-2,3-benzodiazepin-4-one,
7,8-dimethoxy-1-(7-methoxy-2-nathtyl[*sic*])-3,5-dihydro-4*H*-2,3-benzodiazepin-4one,
7,8-dimethoxy-4-methyl-1-phenyl-5*H*-2,3-benzodiazepine,
1-(4-*tert*-butylphenyl)- 7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(2-benzo[b]thienyl)-7-methoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(3-chloro-2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3benzodiazepin-4-one,
1-(4-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(2,4-dichlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(4-iodophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(3-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
1-(5-chloro-2-benzo[b]furyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin4-one, and
1-(4-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one.

The compounds of the invention can be in the form of salts, and in particular acid or base addition salts, which are preferably compatible with a pharmaceutical use. Among pharmaceutically acceptable acids, hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, trifluoroacetic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, tartaric, maleic, citric, ascorbic, methane or ethanesulfonic, and camphoric, acids and the like can be cited in a non-limiting manner. Among pharmaceutically acceptable bases, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine and the like can be cited in a non-limiting manner.

The invention is also directed to a composition which comprises a compound such as defined above and a pharmaceutically acceptable vehicle or excipient.

The compounds or compositions according to the invention can be administered in various manners and in various forms. Thus, they can be injected systemically or orally [*sic*], such as for example intravenously, intramuscularly, subcutaneously, transdermally, intra-arterially, etc., with intravenously, intramuscularly, subcutaneously and orally being preferred. For injections, the compounds are generally prepared in the form of liquid suspensions, which can be injected by means of syringes or drips, for example. In this respect, the compounds are generally dissolved in pharmaceutically compatible saline, physiological, isotonic, buffered solutions, or the like, known to those skilled in the art. Thus, the compositions can contain one or more agents or vehicles chosen from dispersants, solubilizers, stabilizer, preservatives, or the like. Agents or vehicles that may be used in the liquid and/or injectable formulations include in particular methylcellulose, hydroxymethylcellulose, carboxymethylcellulose, polysorbate 80, mannitol, gelatin, lactose, vegetable oils, acacia, and the like.

The compounds can also be administered in the form of gels, oils, tablets, suppositories, powders, gel-capsules, capsules, or the like, optionally by way of pharmaceutical formulations or devices allowing extended and/or delayed release. For this type of formulation, agents such as cellulose, carbonates or starches are advantageously used. It is understood that the rate and/or the injected dose can be adapted by those skilled in the art according to the patient, the pathology in question, the mode of administration, and the like. Typically, the compounds are administered at dosages ranging between 0.1 mg and 100 mg/kg of body weight, more generally from 0.01 to 10 mg/kg, and typically between 0.1 and 10 mg/kg. Moreover, repeated injections can be performed, if necessary. In addition, in the case of chronic treatments, delayed or sustained release systems may be advantageous.

The compounds according to the invention can act on different cyclic nucleotide phosphodiesterases, notably PDE4 and PDE2, and can also be active against certain sub-types of PDE. Thus, four sub-types of the PDE4 have been identified, referred to as PDE4A-D. The compounds of the invention can present particular biological effects according to the sub-type PDE4 affected. Thus, the compounds of the invention can be (selective) inhibiters of PDE-4A, PDE-4B, PDE-4C and/or PDE4D. Compounds of the invention that inhibit PDE-4B are particularly advantageous for the treatment of depression or psychiatric disorders, for example. Some compounds of the invention present the profile of a PDE2 specific inhibiter and have advantageous therapeutic properties for this same reason.

The PDE4 inhibiter compounds according to the invention are particularly advantageous in the treatment of pathologies involving bronchial inflammation and relaxation, and more particularly asthma and chronic obstructive pulmonary disease, as well as other pathologies such as rhinitis, acute respiratory distress syndrome, allergies, skin disorders, such as dermatitis, psoriasis, rheumatoid arthritis, autoimmune diseases, various scleroses (an particularly multiple sclerosis), dyskinesias, glomerulonephritis, osteoarthritis, septic shock or AIDS.

The compounds of the invention are also particularly advantageous for the treatment of inflammatory pathologies of the central nervous system, such as, more specifically, for the treatment of a pathology selected from depression, schizophrenia, bipolar disorder, attention deficit disorder, fibromyalgia, epilepsy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, Lewy body dementia and Crohn's disease.

A particular object of the invention thus resides in the use of compounds such as described hereabove for the preparation of a drug intended for the treatment of disorders of the nervous system, in particular the central nervous system, of a chronic or acute nature.

A more particular object resides in use of compounds as herebefore described for the preparation of a drug intended for the treatment of inflammatory pathologies of the central nervous system (eg. neuroinflammation).

The invention also relates the use of the compounds as anxiolytic, anti-convulsivant or sedative agents, or for the treatment of memory disorders or cognitive disorders.

The invention also relates the use of the above compounds for the treatment of neuro-degenerative pathologies.

In the context of the invention, the term treatment denotes either a preventive or a curative treatment, which may be used alone or in combination with other agents or treatments.

Moreover, this can be a treatment for chronic or acute disorders. The present invention is also directed to the use of the compounds described as anti-inflammatory

agents, for example for treating osteoporosis or rheumatoid arthritis.

The preferred compounds of the invention advantageously have a potent inhibitory action on one or more sub-types of PDE4 and/or an action on PDE2. Moreover, the preferred compounds of the invention present an advantageous selectivity profile, and in particular a weak activity with respect to PDE3.

The compounds of the invention can be prepared starting from commercial products, by implementing a combination of chemical reactions known to those skilled in the art.

In this respect, according to a first process, the compounds of General Formula (I) according to the invention, wherein R_4 is other than chlorine, can be obtained starting from a compound of Formula (I) wherein R_4 is a chlorine atom by implementing the following methods:

1. If R_4 in the formula of the end product is an NR_2R_3 group, by reaction with an amine of formula HNR_2R_3, in a protic solvent at ambient temperature.

Alcohols, and in particular ethanol, can notably be cited as solvents.

2. If R_4 in the formula of the end product is a (C_1-C_6) alkyl group, by reaction with a compound of the formula R_4Li, in an anhydrous solvent at a temperature of between -80 and -20°C, and preferably approximately -78°C.

Ethers, and in particular THF, can be cited as solvents.

3. If R_4 in the formula of the end product is a (C_1-C_6) alkyl group, by reaction with a compound of the formula 1-alkenylcatecholborane, in the presence of a palladium catalyst, in a solvent of the acetonitrile type, at temperature between 50 and 80°C, or by catalytic hydrogenation of compounds where R_4 in the formula of the end product is a C_1-C_6 alkynyl group, using a poisoned catalyst.

4. If R_4 in the formula of the end product is a (C_1-C_6) alkyn-1-yl group, by reaction with a compound of the formula R_4H, in the presence of copper iodide, palladium chloride, triphenyl phosphine, and a base, such as triethylamine. Acetonitrile can, in particular, be used as a solvent; the reaction is preferably carried out at ambient temperature

5. If R_4 in the formula of the end product is a (C_6-C_{12}) aryl group, by reaction with a compound of the formula $R_4B(OH)_2$, potassium phosphate and *tetrakis*(triphenylphosphine)Pd(0), at a temperature of between 80 and 120°C, and preferably approximately 100°C.

As a solvent, the use of an aprotic polar solvent, such as DMF is preferred.

6. If R_4 in the formula of the end product is an OR_2 group, by reaction with an alcohol of formula HOR_2 at ambient temperature; [*sic*]

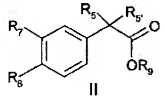
7. If R_4 in the formula of the end product is an SR_2 group, by reaction with a thiol of the formula R_4SH. As a solvent THF can notably be cited.

8. Compounds where R_4 in the formula of the end product is an SH group can be obtained directly by treating compounds in which R_4 is an OH group with Lawesson's reagent.

Compounds of General Formula (I) wherein R_4 represents a chlorine atom can be prepared by reacting a compound of Formula (I') according to the invention with $POCl_3$. This reaction is advantageously carried out in an aprotic polar solvent, such as chloroform, at a temperature of between 90 and 130°C for a time of between 0.5 and 1.5 hours under sealed tube conditions, in the presence of an aromatic amine such as dimethylaniline or dimethylaminopyridine.

The compounds of General Formula (I') according to the invention can be prepared by a process which comprises the following steps:

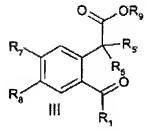
a) reacting a compound of General Formula (II)



II

wherein R_5, R_5, R_7 and R_8 are as defined above and R_8 represents a C_1-C_4 alkyl group, preferably methyl,

with a compound which comprises an acyle group of the formula R_1CO, so as to obtain a compound of Formula (III)



III

wherein R_1, R_5, R_5', R_7 and R_8 are as defined above;

b) reacting the compound of Formula (III) with hydrazine so as to obtain a compound of Formula (I'), wherein R_1, R_5, R_5', R_7 and R_8 are as defined above.

The acylation agent in step a) is preferably an acyl halide, and in particular an acyl chloride.

The reaction is advantageously carried out in the presence of a Lewis acid, such as $SnCl_4$, in an inert solvent at ambient temperature. As solvents, hydrocarbons and their halogen derivatives can be cited, such as $CHCl_3$. At the end of the reaction, the product obtained is taken up in an alcohol, for example methanol, and the reaction is continued at ambient temperature.

Step b) is advantageously carried out in the presence of hydrazine hydrate, for example in an alcohol, at a temperature of between 100 and 150°C preferably approximately 150°C under sealed tube conditions for a time of between 3 and 10 hours, preferably approximately 3 hours, and continued in an acid, for example acetic acid, with reflux, for a period of 20 to 60 minutes.

The invention is illustrated in the examples which follow, which shall be regarded as illustrative and nonrestrictive.

EXAMPLE 1: SYNTHESIS OF COMPOUNDS OF FORMULA I ACCORDING TO THE INVENTION

1.1 Synthesis of the intermediates of Formula III

The following compounds were synthesized:
2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa.
4,5-dimethoxy-2-(2-naphthoyl)phenyl methyl acetate IIIb.
2-(4-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIc.
2-(3-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIId.
2-(2-benzoyl-4,5-dimethoxyphenyl) methyl propionate IIIe.
4,5-dimethoxy-2-(1-oxo-2-phenylethyl)phenyl methyl acetate IIIf
[4,5-dimethoxy-2-(4-phenylbenzoyl)phenyl] methyl acetate IIIg
4,5-dimethoxy-2-(7-methoxy-2-naphthoyl)phenyl methyl acetate IIIh.
2-(5-chloro-2-naphthoyl)-4,5-dimethoxyphenyl methyl acetate IIIi.
2-(2-benzo[b]thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIj.
2-(4-tert-butylbenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIk.
2-(2-benzo[b]thienylcarbonyl)-5-methoxyphenyl methyl acetate IIIl.
2-(3-chlorobenzo[b]thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIm.
2-(4-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIn.
2-(2,4-dichlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIo.
2-(4-iodobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIp.
2-(3-chlorobenzoyl)-4,5-diethoxyphenyl ethyl acetate IIIq.
2-(5-chlorobenzo[b]furylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIr.
2-[2-(2-benzo[b] thienyl)carbonyl-4,5-diethoxyphenyl] ethyl butyrate IIIs.
2-(3-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIt.

2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa.

Add 17.4 ml (124 mmoles) of benzoyl chloride dropwise at 0°C to a solution of 13 g (61.8 mmoles) of 3,4-dimethoxyphenyl methyl acetate in 150 ml of $CHCl_3$. Add 14.5 ml (124 mmoles) of tin (IV) chloride to this solution dropwise. Allow to return to ambient temperature. After 6 hours at ambient temperature, add 100 ml of absolute MeOH slowly and evaporate until dry. Add 400 ml of H_2O and extract 3 times with 400 ml of Et_2O. Dry the organic fractions on Na_2SO_4. Purify by chromatography on silica (AcOEt 1/Hexane 1). Recristallize in EtOH. 16.6 g of colorless crystals are obtained. Yield: 85%.The product can be isolated or used directly in the subsequent reactions.

4,5-dimethoxy-2-(2-naphthoyl)phenyl methyl acetate IIIb.

By replacing the benzoyl chloride with 2-naphthoyl chloride in example IIIa, the title product is obtained in same manner. Yield: 53%.
^{1}H-NMR:
(200 MHz, $CDCl_3$) : δ 3,56 (s, 3H, OCH_3), 3,78 (s, 3H, OCH_3), 3,86 (s, 2H, CH_2), 4,00 (s, 3H, OCH_3), 6,82 (s, 1H Ar), 6,90 (s, 1H Ar), 7,54-8,12 (m, 6H Ar), 8,24 (s, 1H Ar).

2-(4-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIc.

By replacing the benzoyl chloride in example IIIa with 4-chlorobenzoyl chloride, the title product is obtained in same manner.

2-(3-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIId.

By replacing the benzoyl chloride in example IIIa with 3-chlorobenzoyl chloride, the title product is obtained in same manner.

2-(2-benzoyl-4,5-dimethoxyphenyl) methyl propionate IIIe.

By replacing 3,4-dimethoxyphenyl methyl acetate in example IIIa the with 2-(3,4-dimethoxyphenyl) methyl propionate, the title product is obtained in same manner.

4,5-dimethoxy-2-(1-oxo-2-phenylethyl)phenyl methyl acetate IIIf.

By replacing the benzoyl chloride in example IIIa with phenacetyl chloride, the title product is obtained in same manner. Yield: 42%

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,71 (s, 3H, OCH_3), 3,72-3,96 (m, 8H, 2 x OCH_3 + CH_2), 4,26 (s, 2H, CH_2), 6,75 (s, 1H Ar), 7,27-7,41 (m, 6H Ar).

[4,5-dimethoxy-2-(4-phenylbenzoyl)phenyl] methyl acetate IIIg.

By replacing benzoyl chloride in example IIIa with 4-biphenylcarbonyl chloride, the title product is obtained in same manner.

4,5-dimethoxy-2-(7-methoxy-2-naphthoyl)phenyl methyl acetate IIIh.

By replacing benzoyl chloride in example IIIa with 7-methoxy-2-naphthoyl chloride, the title product is obtained in same manner.

2-(5-chloro-2-naphthoyl)-4,5-dimethoxyphenyl methyl acetate IIIi.

By replacing benzoyl chloride in example IIIa with 5-chloro-2-naphthoyl chloride, the title product is obtained in same manner.

2-(2-benzo[b] thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIj.

By replacing the benzoyl chloride in example IIIa with 2-benzo[*b*]thiophene carbonyl chloride, the title product is obtained in same manner. Yield: 58%

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,63 (s, 3H, OCH_3), 3,88 (s, 2H, CH_2), 3,91 (s, 3H, OCH_3), 4,02 (s, 3H, OCH_3), 6,92 (s, 1H Ar), 7,26 (s, 1H Ar), 7,41-7,54 (m, 2H Ar), 7,81 (s, 1H Ar), 7,88-7,98 (m, 2H Ar).

2-(4-tert-butylbenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIk.

By replacing the benzoyl chloride in example IIIa with 4-chloride(*tert*-butyl)benzoyl, the title product is obtained in same manner.

2-(2-benzo[b]thienylcarbonyl)-5-methoxyphenyl methyl acetate IIIl.

By replacing 3,4-dimethoxyphenyl methyl acetate in example IIIj with 3-methoxyphenyl methyl acetate, the title product is obtained in same manner.

2 (3-chlorobenzo[b] thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIm.

By replacing the benzoyl chloride in example IIIa with 2 chloride (3-chlorobenzo[b]thiophene)carbonyl, the title product is obtained in same manner.

2-(4-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIn.

By replacing the benzoyl chloride in example IIIa with 4-bromobenzoyl chloride, the title product is obtained in same manner.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,62 (s, 3H, CH_3), 3,80 (s, 3H, CH_3), 3,85 (s, 2H, CH_2), 3,97 (s, 3H, CH_3), 6,85 (s, 1H Ar), 6,90 (s, 1H Ar), 7,60-7,69 (m, 4H Ar).

2-(2,4-dichlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIo.

By replacing the benzoyl chloride in example IIIa with 2,4-dichlorobenzoyl chloride, the title product is obtained in same manner. Yield: 18%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,71 (s, 3H, CH_3), 3,73 (s, 3H, CH_3), 3,97 (s, 3H, CH_3), 4,00 (s, 2H, CH_2), 6,82 (s, 1H Ar), 6,85 (s, 1H Ar), 7,35-7,38 (m, 2H Ar), 7,48 (s, 1H Ar).

2-(4-iodobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIp.

By replacing the benzoyl chloride in example IIIa with 4-iodobenzoyl chloride, the title product is obtained in same manner.

2-(3-chlorobenzoyl)-4,5-diethoxyphenyl ethyl acetate IIIq.

By replacing 3,4-dimethoxyphenyl methyl acetate in example IIId with 3,4-diethoxyphenyl ethyl acetate, the title product is obtained in same manner.

2-(5-chlorobenzo[b] furylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIr.

By replacing the benzoyl chloride in example IIIa with 5-chlorobenzo[b]furylcarbonyl chloride, the title product is obtained in same manner.

2-[2 (2-benzo[b] thienyl)carbonyl-4,5-diethoxyphenyl] ethyl butyrate IIIs.

By replacing methyl 3,4-dimethoxyphenyl acetate in example IIIj with 2-(3,4-diethoxyphenyl) ethyl butyrate, the title product is obtained in same manner.

2-(3-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIt.

By replacing benzoyl chloride in example IIIa with 3-bromobenzoyl chloride, the title product is obtained in same manner.

1.2. Synthesis of the products of Formula I' (or IV)

The following compounds were synthesized:

7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVa.
7,8-dimethoxy-1-(2-naphthyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVb.
1-(4-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVc.
1-(3-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVd.
7,8-dimethoxy-5-methyl-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVe.
1-benzyl-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVf.
7,8-dimethoxy-1-(4-phenylphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVg.
7,8-dimethoxy-l-(7-methoxy-2-naththyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4one IVh.
1-(5-chloro-2-naphthyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVi.
1-(2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVj.
1-(4-*tert*-butylphenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVk.
1-(2-benzo[b]thienyl)-7-methoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVl.
1-(3-chloro-2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3benzodiazepin-4-one, IVm.
1-(4-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVn.
1-(2,4-dichlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVo.
1-(4-iodophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVp.
1-(3-chlorophenyl)-7,8-diethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVq.
1-(5-chloro-2-benzo[b] furyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin4-one IVr.
1-(benzo[b] thienyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4one IVs.
1-(3-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVt.
7,8-dimethoxy-1-[(3-phenyl) phenyl] -3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVu.

7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVa.

Heat 500 mg (1.59 mmole) of 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa, 2 ml of hydrazine hydrate and 12 ml of EtOH in a sealed tube at 150°C for 3 hours. Allow to return to ambient temperature. Add 10 ml of AcOH. Heat under reflux for 25 minutes. Evaporate until dry. Add 60 ml of glacial H_2O. Allow to crystallize at 0°C for 5 minutes. Filter and wash twice with 5 ml of H_2O, twice with 3 ml of EtOH and twice with 5 ml of pentane. Recristallize in EtOH/Et_2O. Yield : 82%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,51 (s, 2H, CH_2) , 3,72 (s, 3H, OCH_3), 3,97 (s, 3H, OCH_3), 6,67 (s, 1H Ar), 6,86 (s, 1H Ar), 7,43-7,48 (m, 3H Ar), 7,62-7,65 (m, 2H Ar), 8,66 (broad s, 1H exchangeable, NH)

7,8-dimethoxy-1-(2-naphthyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVb

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa, with 4,5-dimethoxy-2-(2-naphthoyl) phenyl methyl acetate IIIb, the title product is obtained in same manner. Yield: 24%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,56 (s, 2H, CH_2) , 3,68 (s, 3H, OCH_3), 4,00 (s, 3H, OCH_3), 6,74 (s, 1H Ar), 6,90 (s, 1H Ar), 7,53-7,60 (m, 2H Ar), 7,82-8,00 (m, 5H Ar), 8,53 (broad s, 1H exchangeable, NH)

1-(4-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVc

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(4-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIc, the title product is obtained in same manner. Yield: 64%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : 3,51 (s, 2H, CH_2), 3,74 (s, 3H, OCH_3), 3,97 (s, 3H, OCH_3), 6,63 (s, 1H Ar), 6,86 (s, 1H Ar), 7,51 (AB system AB, Δδ = 0.17 ppm, J_{AB} = 6 Hz, 4 H Ar) 8,61 (bro ad s, 1H exchangeable, NH)

1-(3-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVd.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(3-chlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIId, the title product is obtained in same manner. Yield: 64% (for both steps). M: 270-273°C

^{1}H-NMR:

(300 MHz, dmso-D_6) : δ 3,45 (s, 2H, CH_2), 3,62 (s, 3H, CH_3), 3,88 (s, 3H, CH_3), 6,65 (s, 1H Ar), 7,13 (s, 1H Ar), 7,47-7,63 (m, 4H Ar), 10,99 (s, 1H exchangeable, NH)

7,8-dimethoxy-5-methyl-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVe

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(2-benzoyl-4,5-dimethoxyphenyl) methyl propionate IIIe, the title product is obtained in same manner. Yield:53% (for the both steps).

^{1}H-NMR:

(300 MHz, dmso-D_6) : δ 1,67 (s large, 3H, CH_3), 3,32-3,37 (m, 1H, H^5), 3,72 (s, 3H, CH_3), 3,98 (s, 3H, CH_3), 6,67 (s, 1H Ar), 6,86 (s, 1H Ar), 7,40-7,51 (m, 3H Ar), 7,64-7,67 (m, 2H Ar), 8,51 (s, 1H exchangeable, NH)

1-benzyl-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVf.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with

4,5-dimethoxy-2-(1-oxo-2-phenylethyl)phenyl methyl acetate IIIf, the title product is obtained in same manner.

^{1}H-NMR:

(200 MHz,

dmso-D_6) : δ 3,14 (s, 2H, $COCH_2$), 3,76 (s, 6H, 2 x OCH_3), 4,18 (s, 2H, CH_2), 6,87 (s, 1H **Ar**), 7,11-7,23 (m, 6H **Ar**), 10,60 (broad s, 1H exchangeable, NH)

7,8-dimethoxy-l-(4-phenylphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one, IVg.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with [4,5-dimethoxy-2-(4-phenylbenzoyl)phenyl] methyl acetate IIIg, the title product is obtained in same manner. Yield: 51%. M:218-221°C.

7,8-dimethoxy-l-(7-methoxy-2-naththyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one, IVh.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 4,5-dimethoxy-2-(7-methoxy-2-naphthoyl)phenyl methyl acetate IIIh, the title product is obtained in same manner. Yield: 39%. M:260-263°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,59 (s, 2H, CH_2), 3,73 (s, 3H, CH_3), (m, 2H **Ar**), 7,70-7,94 (m, 4H **Ar**), 8,44 (broad s, 1H exchangeable, NH)

1-(5-chloro-2-naphthyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVi.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(5-chloro-2-naphthoyl)-4,5-dimethoxyphenyl methyl acetate IIIi, the title product is obtained in same manner. Yield: 51%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,60 (s, 2H, CH_2), 3,72 (s, 3H, CH_3), 4,03 (s, 3H, CH_3), 6,73 (s, 1H **Ar**), 6,93 (s, 1H **Ar**), 7,36-7,45 (m, 1H **Ar**), 7,82-8,31 (m, 5H **Ar**), 8,54 (s, 1H exchangeable, NH)

1-(2-benzo[b] thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVj.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(2-benzo[b]thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIj, the title product is obtained in same manner. Yield: 69%.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,52 (s, 2H, CH_2), 3,84 (s, 3H, CH_3), 3,98 (s, 3H, CH_3), 6,87 (s, 1H **Ar**), 7,13 (s, 1H **Ar**), 7,35-7,44 (m, 3H **Ar**), 7,72-7,91 (m, 2H **Ar**), 8,51 (s, 1H exchangeable, NH)

1-(4-tert-butylphenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4one IVk.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(4-tert-butylbenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIk, the title product is obtained in same manner. Yield: 41%. M: 214°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 1,37 (s, 9H, 3 x CH_3), 3,49 (s, 2H, CH_2), (s, 1H exchangeable, NH)

1-(2-benzo[b] Ithienyl)-7-methoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVl.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(2-benzo[b] thienylcarbonyl)-5-methoxyphenyl methyl acetate IIIl, the title product is obtained in same manner. Yield: 18%. M: 264°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,57 (s, 2H, CH_2), 3,91 (s, 3H, CH_3), 6,91-7,00

(m, 2H Ar), 7,32-7,45 (m, 3H Ar), 7,59-7,63 (m, 1H Ar), 7,72-7,75 (m, 1H Ar),

7,86-7,88 (m, 1H Ar), 8,42 (s, 1H exchangeable, NH)

1-(3-chloro-2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3benzodiazepin -4-one, IVm.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(3-chlorobenzo[b] thienylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIm, the title product is obtained in same manner. Yield: 18%.

1-(4-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVn.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(4-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIn, the title product is obtained in same manner. Yield: 61 %.

1-(4-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVn.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(4-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIn, the title product is obtained in same manner. Yield: 29%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,50 (s, 2H, CH_2), 3,74 (s, 3H, CH_3), 3,97 (s, 3H, CH_3), 6,63 (s, 1H Ar), 6,85 (s, 1H Ar), 7,50-7,59 (m, 4H Ar), 8,41 (s, 1H exchangeable, NH)

1-(2,4-dichlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4one IVo.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(2,4-dichlorobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIo, the title product is obtained in same manner. Yield: 12%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,60 (s, 2H, CH_2), 3,69 (s, 3H, CH_3), 3,96 (s, 3H, CH_3), 6,37 (s, 1H Ar), 6,84 (s, 1H Ar), 7,40-7,60 (m, 3H Ar), 8,51 (s, 1H exchangeable, NH)

1-(4-iodophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVp.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(4-iodobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIp, the title product is obtained in same manner. Yield: 62%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,50 (s, 2H, CH_2), 3,74 (s, 3H, CH_3), 3,97 (s, 3H, CH_3), 6,63 (s, 1H Ar), 6,85 (s, 1H Ar), 7,36-7,80 (m, 4H Ar), 8,57 (s, 1H exchangeable, NH)

1-(3-chlorophenyl)-7,8-diethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVq.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(3-chlorobenzoyl)-4,5-diethoxyphenyl ethyl acetate IIIq, the title product is obtained in same manner. Yield: 24% (for both steps). M: 182-183°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 1,37 (t, 3H, CH_3), 1,51 (t, 3H, CH_3), 3,48 (s, 2H, CH_2), 3,92 (q, 2H, CH_2), 4,17 (q, 2H, CH_2), 6,64 (s, 1H Ar), 6,83 (s, 1H Ar), 7,33-7,50 (m, 3H Ar), 7,65 (d, 1H Ar), 8,58 (s, 1H exchangeable, NH)

1-(5-chloro-2-benzo[b]furyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3benzodiazepin-4-one IVr.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(5-chlorobenzo[b]furylcarbonyl)-4,5-dimethoxyphenyl methyl acetate IIIr, the title product is obtained in same manner. Yield: 33%. M: 249-252°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,53 (s, 2H, CH_2), 3,87 (s, 3H, CH_3), 3,99 (s, 3H, CH_3), 6,87 (s, 1H Ar), 7,00 (s, 1H Ar), 7,10 (s, 1H Ar), 7,35-7,39 (m, 1H Ar), 7,53-7,62 (m, 2H Ar), 8,76 (s, 1H exchangeable, NH)

1 (benzo lb]thienyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVs.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-[2-(2-benzo[b]thienyl)carbonyl-4,5-diethoxyphenyl] ethyl butyrate IIIs, the title product is obtained in same manner. Yield: 23%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 1,11 (t, J = 6,21, 3H, CH_3), 1,40-1,46 (m, 3H, CH_3), 1,53 (t, J = 7,92, 3H, CH_3), 1,96-2,43 (m, 2H, CH_2), 3,02-3,07 (t, J = 6,01, 1H, H^5), 4,04-4,24 (m, 4H, 2 x CH_2), 6,83 (s, 1H Ar), 7,15 (s, 1H Ar), 7,35-7,90 (m, 5H Ar), 8,39 (s, 1H exchangeable, NH)

1-(3-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVt.

By replacing 2-benzoyl-4,5-dimethoxyphenyl methyl acetate IIIa in example IVa with 2-(3-bromobenzoyl)-4,5-dimethoxyphenyl methyl acetate IIIt, the title product is obtained in same manner. Yield: 30%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,51 (s, 2H, CH_2) , 3,75 (s, 3H, OCH_3), 3,98 (s, 3H, OCH_3), 6,64 (s, 1H Ar), 6,85 (s, 1H Ar), 7,28-7,84 (m, 4H Ar), 8,47 (broad s, 1H exchangeable, NH)

7,8-dimethoxy-1-[(3-phenyl)phenyl]-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVu.

Heat a mixture of 100 mg (0.267 mmole) of 1-(3-bromophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVt, 44 mg (0.356 mmole) of phenylboronic acid, 30 mg of *tetrakis*-triphenylphosphine Pd(0), 251 µl of Na_2CO_3 and 291 µl of EtOH in 5 ml of toluene to 90°C for 12 hours. Evaporate until dry. Purify by chromatography (AcOEt/Hexane 1/1). Recristallize in EtOH. Yield: 61%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,52 (s, 2H, CH_2) , 3,72 (s, 3H, OCH_3), 3,96 (s, 3H, OCH_3), 6,72 (s, 1H Ar), 6,86 (s, 1H Ar), 7,38-7,69 (m, 9H Ar), 8,80 (bro ad s, 1H exchangeable, NH)

EXAMPLE 2: SYNTHESIS OF COMPOUNDS OF GENERAL FORMULA I

2.1. Synthesis of Compounds of Formula (I) wherein R_4 is a chlorine atom (compounds of Formula V)

4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Va.

Heat a mixture of 150 mg (0.51 mmole) of 7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVa, 200 µl of dimethylaniline and 500 µl of $POCl_3$ in 10 ml of $CHCl_3$ in a sealed tube for 45 minutes at 120°C. Allow to return to ambient temperature. Evaporate until dry. Add 30 ml of AcOEt and 3 ml of triethylamine. Evaporate until dry. Purify by chromatography [(]AcOEt 1/Hexane 4 then AcOEt 1/Hexane 1). Triturate in 3 ml of Et_2O. Filter. Wash with twice 3 ml of pentane. Yield: 57%.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 3,54-3,65 (m, 2H, CH_2), 3,77 (s, 3H, CH_3), 4,02 (s, 3H, CH_3), 6,80 (s, 1H Ar), 6,82 (s, 1H Ar), 7,42-7,50 (m, 3H Ar), 7,68-7,70 (m, 2H Ar).

4-chloro-1-(3-chlorophenyl)-7,8-dimethoxy-5*H*-2,3-benzodiazepine Vb.

By replacing 7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVa in example Va with 1-(3-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVd, the title product is obtained in same manner.

2.2. Synthesis of Products of Formula (I)

The following compounds were synthesized:

4-n-butyl-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Ia.
7,8-dimethoxy-4-methylamino-1-phenyl-5*H*-2,3-benzodiazepine Ib.
7,8-dimethoxy-1-phenyl-4-(pyrrolidin-1-yl)-5*H*-2,3-benzodiazepine Ic.
1-(3-chlorophenyl)-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine Id.
7,8-dimethoxy-4-(*N,N*-dimethylamino)-1-phenyl-5*H*-2,3-benzodiazepine Ie.
7,8-dimethoxy-1-phenyl-4-propylamino-5*H*-2,3-benzodiazepine If.
7,8-dimethoxy-4-(1-morpholino)-1-phenyl-5*H*-2,3-benzodiazepine Ig.
4-(2-hydroxyethylamino)-7,8-dimethoxy-1-phenyl-5*H*-2, 3-benzodiazepine Ih.
7,8-dimethoxy-4-(1-heptynyl)-1-phenyl-5*H*-2, 3-benzodiazepine Iz.
7,8-dimethoxy-1-phenyl-4-(prop-1-ynyl)-5*H*-2,3-benzodiazepine Ii.
7,8-dimethoxy-1-phenyl-4-*n*-propyl-5*H*-2,3-benzodiazepine Ij.
4,7,8-trimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Il.
7,8-dimethoxy-4-methyl-1-phenyl-5*H*-2,3-benzodiazepine Im.
7,8-dimethoxy-4-(4-methylphenyl)-1-phenyl-5*H*-2,3-benzodiazepine In.

4-n-butyl-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Ia.

Under an inert atmosphere at -78°C, add 360 µl of 1.6 M *n*-BuLi in THF to a solution of 150 mg (0.48 mmole) of 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine in 7 ml of anhydrous THF. Allow to return to ambient temperature. After 5 minutes, add 3 drops of AcOH. Evaporate until dry. Purify by chromatography on silica (AcOEt 1/Hexane 1). Recristallize in CH_2Cl_2/pentane. 133 mg of colorless crystal is obtained. Yield: 83%. M:140-142°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 0,91 (t, J = 7,33, 3H, CH_3), 1,23-1,37 (m, 2H, CH_2CH_3), 1,57-1,69 (m, 2H, $CH_2CH_2CH_3$), 2,42-2,48 (m, 2H, $CH_2(CH_2)_2CH_3$), 3,16(AB system δ = 0,32, J_{AB} = 12,4, 2H, CH_2), 3,73 (s, 3H, CH_3), 3,98 (s, 3H, CH_3), 6,74 (s, 1H Ar), 6,81 (s, 1H Ar), 7,40-7,46 (m, 3H Ar), 7,71-7,74 (m, 2H Ar).

7,8-dimethoxy-4-methylamino-1-phenyl-5*H*-2,3-benzodiazepine Ib.

Place a mixture of 50 mg (0.159 mmole) of 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Va, 2 ml (2 mmoles) of 1M methylamine in THF and 8 ml of EtOH under agitation at ambient temperature for 12 hours. Evaporate until dry. Add 10 ml of a saturated solution of $NaHCO_3$ and 20 ml of H_2O and extract 3 times with 20 ml of AcOEt. Dry the organic fractions on Na_2SO_4. Evaporate until dry. Recristallize in EtOH/Et2O. Yield: 89 %. M:212-215°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 2,87 (s, 3H, CH_3), 3,02-3,29 (m, 2H, CH_2), 3,73 (s, 3H, CH_3), 3,96 (s, 3H, CH_3), 6,68 (s, 1H **Ar**), 6,78 (s, 1H **Ar**), 7,35-7,41 (m, 3H **Ar**), 7,68-7,74 (m, 2H **Ar**).

7,8-dimethoxy-1-phenyl-4-(pyrrolidin-1-yl)-5*H*-2,3-benzodiazepine Ic.

By replacing methylamine in example Ib with pyrrolidine, the title product is obtained in same manner. Yield: 67%.mF:228-230°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 1,89-1,97 (m, 4H, **(CH_2)$_2$) pyrrolidine**), 3,09-3,76 (m, 9H, **N(CH_2)$_2$) pyrrolidine** + CH_2), 3,73 (s, 3H, CH_3), 3,96 (s, 3H, CH_3), 6,76 (s, 1H **Ar**), 6,79 (s, 1H **Ar**), 7,35-7,39 (m, 3H **Ar**), 7,69-7,74 (m, 2H **Ar**).

1-(3-chlorophenyl)-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine, Id.

By replacing 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Va in example Ia with 4-chloro-1-(3-chlorophenyl)-7,8-dimethoxy-5*H*-2,3benzodiazepine Vb, and replacing the *n*-BuLi by with MeLi, the title product is obtained in same manner. (girisopam)

7,8-dimethoxy-4-(NR, N-dimethylamino)-1-phenyl-5*H*-2,3-benzodiazepine Ie.

By replacing methylamine in example Ib with dimethylamine, the title product is obtained in same manner. Yield: 88%. MF:182-184°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,06 (s, 6H, N(CH_3)$_2$), 3,38 (système AB, $\delta = 0,79$, J_{AB} = 8,8, 2H, CH_2), 3,75 (s, 3H, CH_3), 3,97 (s, 3H, CH_3), 6,76 (s, 1H **Ar**), 6,81 (s, 1H **Ar**), 7,38-7,40 (m, 3H **Ar**), 7,71-7,75 (m, 2H **Ar**).

7,8-dimethoxy-1-phenyl-4-propylamino-5*H*-2,3-benzodiazepine If.

By replacing methylamine in example Ib with N-propylamine, the title product is obtained in same manner. Yield: 76%. M:202-204°C.

7,8-dimethoxy-4-(1-morpholino)-1-phenyl-5*H*-2,3-benzodiazepine Ig.

By replacing methylamine in example Ib with the morpholine, the title product is obtained in same manner. Yield: 87%. M:200-202°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,32 (système AB, $\delta = 0,67$, J_{AB} = 13,4, 2H, CH_2), 3,34-3,56 (m, 4H, 2 x CH_2), 3,72-3,76 (m, 7H, 2 x CH_2 + CH_3), 3,97 (s, 3H, CH_3), 6,69 (s, 1H **Ar**), 6,81 (s, 1H **Ar**), 7,38-7,41 (m, 3H **Ar**), 7,70-7,73 (m, 2H **Ar**).

4 (2-hydroxyethylamino)-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Ih.

By replacing methylamine in example Ib with 2-hydroxyethylamine, the title product is obtained in same manner. Yield: 76%. M:211-213°C.

7,8-dimethoxy-4-(1-heptynyl)-1-phenyl-5*H*-2,3-benzodiazepine Iz.

Place a mixture of 100 mg (0.318 mmole) of 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Va, 12 mg of CuI, 7 mg of $PdCl_2$, 23 mg of triphenylphosphine,1 ml of triethylamine, and 300 µl of 1-heptyne in 4 ml of CH_3CN under agitation at ambient temperature for 2 hours. Evaporate until dry. Purify by chromatography (AcOEt 1/Hexane 4 then AcOEt 1/Hexane 2). 344 mg of a yellow oil is obtained, which crystallizes slowly. Yield: 92%. M:38°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 0,92 (t, J = 7,02, 3H, CH_3), 1,31-1,47 (m, 4H, $(CH_2)_2$), 1,55-1,64 (m, 2H, CH_2), 2,38 (t, J = 7,0, 2H, CH_2), 3,29(AB system, δ = 0,32, J_{AB} = 12,5, 2H, CH_2), 3,75 (s, 3H, CH_3), 3,99 (s, 3H, CH_3), 6,79 (s, 1H Ar), 6,80 (s, 1H Ar), 7,39-7,46 (m, 3H Ar), 7,69-7,71 (m, 2H Ar).

7,8-dimethoxy-1-phenyl-4-(prop-1-ynyl)-5*H*-2,3-benzodiazepine Ii.

By replacing 1-heptyne in example Iz with 1-propyne condensed at 78°C in a sealed tube, the title product is obtained in same manner. Yield: 72%. M: 139-141°C.

^{1}H-NMR:

(300 MHz, $CDCl_3$) : δ 2,04 (s, 3H, $CH_3C\equiv C$), 3,29 (AB system, δ = 0,33, J_{AB} = 12,5, 2H, CH_2), 3,75 (s, 3H, CH_3), 4,00 (s, 3H, CH_3), 6,80 (s, 2H Ar), 7,40-7,46 (m, 3H Ar), 7,69-7,72 (m, 2H Ar).

7,8-dimethoxy-1-phenyl-4-*n*-propyl-5*H*-2,3-benzodiazepine Ij.

Hydrogenate 70 mg (0.22 mmole) of 7,8-dimethoxy-1-phenyl-4-(prop-1-ynyl)-5*H*-2,3-benzodiazepine Ii in 10 ml of MeOH in the presence of 30 mg of Pd/C, at ambient temperature, under atmospheric pressure for 4 hours. Evaporate until dry. Purify by chromatography on silica (AcOEt 1/Hexane 1). Recristallize in CH_2Cl_2/pentane. 57 mg of the title product is obtained in the form of colorless crystals. Yield: 81%. M: 129-133°C.

(200 MHz, $CDCl_3$) : δ 0,91 (t, J = 7,33, 3H, CH_3), 1,59-1,75 (m, 2H, CH_2CH_3), 2,38-2,46 (m, 2H, $CH_2CH_2CH_2$), 3,15(AB system, δ = 0,33, J_{AB} = 12,5, 2H, CH_2), 3,75 (s, 3H, CH_3), 3,98 (s, 3H, CH_3), 6,73 (s, 1H Ar), 6,80 (s, 1H Ar), 7,40-7,44 (m, 3H Ar), 7,69-7,74 (m, 2H Ar).

4,7,8-trimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Il.

Place a solution of 100 mg (0.318 mmole) of 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine in 10 ml of MeOH at ambient

temperature, under an inert atmosphere. Evaporate until dry. Add 10 ml of a saturated solution of $NaHCO_3$ and 10 ml of H_2O. Extract twice with 20 ml of AcOEt. Dry the organic fractions on Na_2SO_4. Recristallize in Et2O. Yield: 73%.

7,8-dimethoxy-4-methyl-1-phenyl-5*H*-2,3-benzodiazepine Im.

By replacing *n*-BuLi in example Ia with MeLi, the title product is obtained in same manner. Yield: 67%. M:144-146°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) :

δ 2,20 (s, 3H, CH_3), 3,19 (système AB, $\Delta\delta = 0,24$, $J_{AB} = 12,2$, CH_2), 3,78 (s, 3H, CH_3), 4,02 (s, 3H, CH_3), 6,78 (s, 1H Ar), 6,84 (s, 1H Ar), 7,42-7,48 (m, 3H Ar), 7,73-7,78 (m, 2H Ar).

7,8-dimethoxy-4-(4-methylphenyl)-1-phenyl-5*H*-2,3-benzodiazepine In.

Heat a mixture of 200 mg (0.64 mmole) of 4-chloro-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine Va, 100mg (0.74 mole) of 4-methylbenzene boronic acid, 152 mg (0.72 mmole) of K_3PO_4 and 23 mg of *tetrakis*-triphenylphosphine palladium (0) in 5 ml of DMF to 105°C under an inert atmosphere for 16 hours. Add 30 ml of H_2O and extract 3 times with 30 ml of AcOEt. Dry the organic fractions on Na_2SO_4. Evaporate until dry. Purify by chromatography (AcOEt 1/Hexane 1). Yield: 23%.

^{1}H-NMR:

(300 MHz, $CDCl_3$)

: δ 2.40 (s, 3H, CH_3), 3.61 (AB system, $\Delta\delta = 0,91$, $J_{AB} = 12,8$, CH_2), 3,74 (s, 3H, CH_3), 3,98 (t, J = 7,91, 3H, CH_3), 6,84 (s, 2H Ar), 6,84 (s, 1H Ar), 7,16-7,79 (m, 9H Ar).

EXAMPLE 3: SYNTHESIS COMPOUNDS OF FORMULA 1 WHEREIN R_4 IS AN SH GROUP

4-mercapto-7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepine, Io

Heat a mixture of 80 mg (0.27 mmole) of 7,8-dimethoxy-1-phenyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one IVa and 60 mg of Lawesson's reagent in 15 ml of anhydrous toluene under reflux for 12 hours. Allow to return to ambient temperature. Evaporate until dry. Purify by chromatography (AcOEt/Hexane 1/4 then 1/1). Recristallize in AcOEt. Yield: 69%. M:166-168°C.

^{1}H-NMR:

(200 MHz, $CDCl_3$) : δ 3,71 (s, 3H, CH_3), 3,89 (s, 2H, CH_2), 3,89 (s, 3H, CH_3), 6,63 (s, 1H Ar), 6,88 (s, 1H Ar), 7,43-7,66 (m, 5H Ar), 10,15 (s, 1H exchangeable, NH)

EXAMPLE 4: PHARMACOLOGICAL ACTIVITY: INHIBITION OF PHOSPHODIESTERASES.

4.1. Isolation of phosphodiesterases from smooth muscle

A 3 g segment of bovine aortic media cut into pieces with scissors was homogenized with an Ultra-Turrax, then with a glass/glass Potter, in 7 volumes/weight of buffer A, containing a protease inhibitor cocktail (20 mM Tris-HCl, 0.25 M saccharose, 2 mM magnesium acetate, 1 mM dithiothreitol, 5 mM EGTA, 2000 U/ml aprotinin, 10 mg/l leupeptin and 10 mg/l soya trypsic inhibitor). The homogenate was centrifuged for 1h at 105000 g. The supernatant was loaded on a DEAE-Sephacel [column] (15 x 1.6 cm) pre-equilibrated with buffer B (buffer A without saccharose, EGTA or protease inhibitors). The column was washed until no absorption could be detected at 280 nm, then eluted with a linear NaCl gradient (0-0.5M) in the buffer B. 3 ml fractions were collected and enzyme activities were determined under the conditions described hereafter so as to localize the various enzymes PDE1, PDE3, PDE4 and PDE5, which were aliquoted and frozen at -80° C. (Lugnier *et al.*, Biochem. Phamacol., 35 (1986) 1746 1751). PDE2 was prepared from bovine endothelial cells by the same methods (Lugnier and Schini, Biochem. Pharmacol. 1990, 39; 75 84).

4.2. Protocol for Measurement of Phosphodiesterasic Activities

Cyclic nucleotide phosphodiesterase activity was determined by a radioenzymatic method using tritiated cyclic GMP or AMP (1 µM) as a substrate (Lugnier *et al.*, 1986). Adenosine or the tritiated guanosine monophosphate formed by hydrolysis of the labeled cyclic nucleotide was converted to tritiated adenosine or guanosine, in a second incubation with one nucleotidase in excess. The nucleoside produced was separated from the nucleotides by chromatography on an anion exchange resin. The radioactivity of the nucleoside was determined by liquid scintillation. Enzymatic incubations were carried out under conditions such that there was no more than 15% hydrolysis of the substrate, with each point being performed in duplicate.

4.2.1. Determination of PDE4 inhibition.

The concentration of substance which inhibits enzymatic activity by 50% (IC_{50}) at 1 µM of cyclic AMP was calculated by nonlinear regression (Prism, GraphPad).

4.2.2. Selectivity

An evaluation was carried out for the activity of the compounds on other phosphodiesterase isoforms, and particularly PDE1 from vascular smooth muscle in the basal state or activated by calmodulin, PDE2 from vascular endothelial cells in the basal state or activated by cyclic GMP, PDE3 andPDE5 from vascular smooth muscle.

The results obtained are shown in Tables 1 to 3 hereafter, where % indicates the percentage of inhibition of the enzymatic activity produced by 10 µmoles of the compound tested.

Table 1
Compounds of General Formula (I').

Example	PDE4 CI_{50} (μM) or percentage of inhibition at 10 μM.
IVa	7.7
IVb	1.5
IVc	1.5
IVe	8.8
IVf	36%
IVg	2.7
IVh	7.0
IVi	1.2
IVj	1.2
IVk	3.4
IVm	14
IVn	3.9
IVo	31%
IVp	2.9
IVd	7.7
IVr	31
IVu	2.6
IVq	0.73
IVs	0.083
IVl	11%

Table 2
Compounds of General Formula (I), R_5' = H.

name	PDE4 CI_{50} (μm) or percentage of inhibition at 10 μm
tofisopam	0.68
Id (girisopam)	3.2
Ib	20%
Ic	12%
Ie	16%
If	16%
Ig	15%
Ih	27%
Ii	21%
Ij	21
Ia	31%
Il	24%
Im	13.6
Io	3.4

Table 3
Selectivity

name	CI_{50} or percentage of inhibition at 10μm				
	PFR 1	**PDE 2**	**PDE 3**	**PDE 4**	**PDE 5**
IVb	71%	17	4.5	1.5	38%
IVc	62%	8.5%	-	1.5	23%
IVg	50%	16%	82%	2.7	51%
IVi	69%	66%	86%	1.2	58%
IVj	70%	38%	73%	1.2	54%
IVu	46%	38%	89%	2.6	39%
xxxxx	-	0.9	6	0.68	33
Id xxx	-	4	22%	3.2	13
Io	-	11	138%	3.4	17
IVq	51%	11%	63%	0.73	62%
IVs	45%	22%	59%	0.083	44%

All of the compounds tested show a strong PDE4 inhibitory action. The preferred compounds according to the invention present an excellent potency and selectivity profile with respect to phosphodiesterase 4, insofar as these compounds more weakly inhibit the other PDEs, and in particular PDE3.

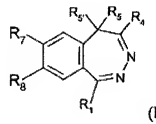
EXAMPLE 5:ANTI-INFLAMMATORY PROPERTIES OF COMPOUNDS OF THE INVENTION

Compounds according to the invention were evaluated for anti-inflammatory properties on mononuclear cells from venous blood of healthy donors (n=4), according to a protocol approved by the Alsace No. 1 Consultation Committee for Protection of Persons in Biomedical Research. More specifically, the cells were incubated for 24 hours (24-well plate) in the presence of the compound tested, after activation by Salmonella Abortis Equi Lipopolysaccharide (LPS) (5μg/ml) and by Phytohemagglutinin (PHA,1 μg/ml) (cf. De Groote *et al. Cytokine* 4,1992, 239). After incubation, the concentrations of TNFa in the culture supernatants were measured by the ELISA method (Antibody Solutions, Half Moon Bay, CA, USA).

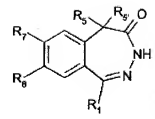
The results found show a marked dose dependent inhibition of the production of TNFα, and only TNFα (compared to IL1β, IL6 and IL8 which were not significantly decreased) by the compounds tested. For example, compound IVs returns the measured TNFα levels to basal levels after activation of the cells, starting at 1 uM.

CLAIMS

1. Use of compounds of General Formula (I) or (I')



(I)



(I')

wherein:

R_1 is a (C_1-C_8) alkyl group, (C_3-C_8) cycloalkyl group, (C_6-C_{18}) group, (C_6-C_{18})aryl(C_1-C_4)alkyl group, (C_1-C_8)alkyl(C_6-C_{18})aryl group, (C_5-C_{18}) heteroaryl group comprising 1 to 3 heteroatoms, or a OR_2, SR_2 or NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom, a (C_1-C_8) alkyl group, (C_3-C_8)cycloalkyl(C_6-C_{12})aryl group or (C_5-C_{12}) heteroaryl group comprising 1 to 3 heteroatoms; or (ii) R_2 and R_3 together form a straight or branched hydrocarbon chain having from 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally interrupted by a nitrogen, sulfur or oxygen atom;

R_4 is a halogen atom or a (C_1-C_8) alkyl, (C_2-C_8) alkyl, (C_2-C_8) alkynyl, or phenyl group or a OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined above;

R_5 and R_5', independently of each other, are selected from a hydrogen atom, a (C_1-C_8) alkyl group, a phenyl group, a substituted phenyl group or a (C_1-C_8) alkylphenyl group, which may or may not be substituted, or, R_5 and R_5' together form a straight or branched hydrocarbon chain having from 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally interrupted by a nitrogen or sulfur, oxygen atom;

R_7 and R_8, independently of each other, are selected from a hydrogen atom and a OR_2 group, R_2 being as defined above,

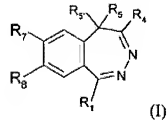
the alkyl, cycloalkyl, aryl, heteroaryl, alkyl and alkynyl groups and the hydrocarbon chain defined above, optionally substituted by one or more identical or different substituents, preferably selected from a halogen atom, an OH, =O, NO_2, NH_2, CN, COOH or CF_3 group, a (C_1-C_8) alkoxy group and a $NHCOR_2$ or $CONR_2R_3$ group, wherein and R_2 and R_3 are as defined above,

for the preparation of a pharmaceutical composition intended to inhibit a cyclic nucleotide phosphodiesterase, and in particular of phosphodiesterase 4 (PDE4).

2. A compound of General Formula (I) or (I') as defined in claim 1, wherein R_4, R_5, R_5, R_7 and R_8 as are as defined in claim 1 and R_1 is a (C_1-C_8) alkyl group, (C_3-C_8) cycloalkyl group, (C_1-C_8)alkyl(C_6-C_18)aryl group, or a (C_5-C_{18}) heteroaryl group comprising 1 to 3 heteroatoms, or a OR_2, SR_2 or NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom, a (C_1-C_8)alkyl group, (C_3-C_8)

cycloalkyl(C_6-C_{12})aryl group, or a (C_5-C_{12}) heteroaryl group comprising 1 to 3 heteroatoms; or (ii) R_2 and R_3 together form a straight or branched hydrocarbon chain having from 2 to 6 carbon atoms, optionally comprising one or more double bonds and/or optionally interrupted by a nitrogen, sulfur or oxygen atom.

3. A compound of General Formula (I) or (I')



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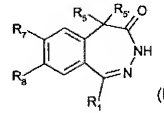
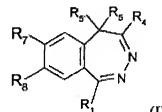


(I')

wherein R_1, R_4, R_5, R_5', R_7 and R_8 as are defined in claim 1, excluding compounds of Formula (I) wherein R_5 represents a substituted phenyl or (C_1-C_6) alkyl radical and R_5 represents an hydrogen atom, and excluding compounds of Formula (I) wherein R_5 and R_5, simultaneously represent a hydrogen atom, in particular when R_7 and R_8 represent a methoxy group and R_1 represents a diethoxyphenyl or 3-chlorophenyl group.

4. A compound of General Formula (I) or (I')



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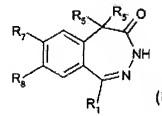
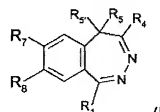


(I')

wherein R_4, R_5, R5, R_7 and R_8 are as defined in claim 1 and R_1 is a heteroaryl group.

5. A compound of General Formula (I) or (I')



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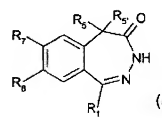
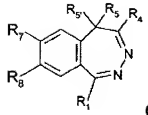


(I')

wherein R_1, R_4, R_5 and R'$_5$ [*sic*] are as defined in claim 1 and R_7 and R_8 represent an, ethoxy group, with the exception of the compound 1-(2-chlorophenyl)-4-methyl-7,8-diethoxy-5*H*-2,3-benzodiazepine.

6. A compound of Formula (I) according to claim 5 wherein R_4 and R_5 represent a hydrogen atom or a (C_1-C_6) alkyl radical, R_4 and R_5 not [each] simultaneously being an hydrogen atom, and R_5 preferably representing a (C_1-C_6) alkyl radical.

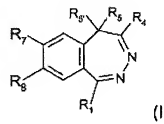
7. A compound of General Formula (I)



(I)

wherein R_1, R_5, R'_5 [*sic*] , R_7 and R_8 are as defined in claim 1 and R_4 is a halogen atom, a (C_2-C_6) alkyl, (C_2-C_6) alkynyl, or phenyl group or an OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined in claim 1.

8. A compound of General Formula (I) or (I')



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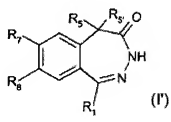


(I')

wherein R_4, R_5, R'_5 [*sic*] , R_7 and R_8 are as defined in claim 1 and R_1 is: (i) a (C_1-C_6) alkyl group, (C_3-C_6) cycloalkyl group, or (C_5-C_i2) heteroaryl group comprising 1 to 3 heteroatoms; or (ii) an OR_2, SR_2 or NR_2R_3 group wherein R_2 and R_3 are as defined in claim 1.

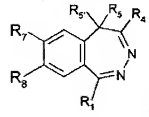
9. A compound of General Formula (I) as defined in claim 1, characterized in that R_4 is selected from a halogen atom, and preferably chlorine, a (C_2-C_6) alkynyl group, or a NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom, a (C_1-C_6) alkyl or a (C_1-C_6) hydroxyalkyl group; or (ii) R_2 and R_3 together form a chain of the formula $-(CH_2)_m-(O)_n-(CH_2)_2-$ wherein m is an whole number from 2 to 3 and n is equal to 0 or 1.

10. A compound of General Formula (I) as defined in claim 1, characterized in that R_4 represents an NR_2R_3 group wherein: (i) R_2 represents a hydrogen atom and R_3 is selected from a (C_1-C_6) alkyl or (C_1-C_6) hydroxyalkyl group: or (ii) R_2 and R_3 together form a chain of the formula $(CH_2)_m-(O)_n-(CH_2)_2$ wherein m is an whole number from 2 to 3, and preferably equal to 2, and n is equal to 0 or 1.

11. A compound of General Formula (I') as defined in claim 1, characterized in that R_1 is a substituted phenyl group or an optionally substituted naphtyl group.

12. A compound of General Formula (I) according to claim 1, characterized in that R_1 is an unsubstituted phenyl group, R_4 is a halogen, a (C_2-C_6) alkyl or (C_2-C_6) alkynyl group, or an NR_2R_3 group wherein: (i) R_2 and R_3, independently of each other, are selected from a hydrogen atom or a (C_1-C_6) alkyl group; or (ii) R_2 and R_3 together form a $(CH_2)_n$ group, n being a whole number between 3 and 6 inclusive, or a $(CH_2)_2(O)(CH_2)_2$ group, R_5 and R_5' are [each] a hydrogen atom and R_7 and R_8 [each] represent an OMe group.

13. A compound of General Formula (I) or (I')



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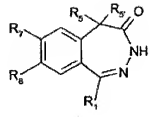


(I')

wherein R_1 is a heteroaryl group, R_7 and R_8 [each] represent a, ethoxy group, and R_4, R_5 and R'_5 [*sic*] are as defined in claim 1.

14. A compound according to claim 13, characterized in that R_4 is a (C_1-C_3) alkyl group, R_5 is a hydrogen atom or a (C_1-C_3) alkyl group, and R_5' is a hydrogen atom.

15. A compound according to [any] one of claims 2 to 14 selected from the following compounds:

-7,8-dimethoxy-1-(2-naphthyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1-(4-chlorophenyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-7,8-dimethoxy-1-(4-phenylphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1-(5-chloro-2-naphtyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1 (2-benzo[b]thienyl)-7,8-dimethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1-(3-chlorophenyl)-7,8-diethoxy-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1-(benzo[b]thienyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4one,
-7,8-dimethoxy-1-(3-phenylphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one,
-1-(benzo[b]thienyl)-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine,
-1-(benzo[b]thienyl)-7,8-diethoxy-4-methyl-5*H*-2,3-benzodiazepine,
1-(2-benzo[b]thienyl)-7,8-diethoxy-5-*n*-propyl-3,5-dihydro-4*H*-2,3benzodiazepin-4-one,
1-(cinnamyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one
7,8-diethoxy-5-ethyl-1-(2-fluorophenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one
1-(2-chlorophenyl)-7,8-diethoxy-5-ethyl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one
7,8-diethoxy-5-ethyl-1-(2-hydroxyphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one
7,8-diethoxy-5-ethyl-1-(2-methoxyphenyl)-3,5-dihydro-4*H*-2,3-benzodiazepin-4-one
1-(2-benzo[b]thienyl)-7,8-diethoxy-4-methyl-5-N-propyl-5*H*-2,3-benzodiazepine
1-(cinnamyl)-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine
7,8-diethoxy-5-ethyl-1-(2-fluorophenyl)-4-methyl-5*H*-2,3-benzodiazepine
1-(2-chlorophenyl)-7,8-diethoxy-5-ethyl-4-methyl-5*H*-2,3-benzodiazepine
7,8-diethoxy-5-ethyl-1-(2-hydroxyphenyl)-4-methyl-5*H*-2,3-benzodiazepine
7,8-diethoxy-5-ethyl-1-(2-methoxyphenyl)-4-methyl-5*H*-2,3-benzodiazepine
and salts thereof.

16. A composition comprising a compound according to [any] one of claims 2 to 15 and a pharmaceutically acceptable vehicle or excipient.

17. Use of a compound according to [any] one of claims 2 to 15 for the preparation of a drug intended for the treatment of a central nervous system pathology.

18. Use of a compound according to [any] one of claims 2 to 15 for the preparation of a drug intended for the treatment of neuroinflammation.

19. Use of a compound according to [any] one of claims 2 to 15 for the preparation of a drug intended for the treatment of depression.

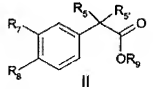
20. A method of preparing a compound according to one of claims 1 to 15, comprising reacting a compound of Formula (I) wherein R_4 is a chlorine atom with:

- if R_4 is a NR_2R_3 group, a compound of the formula HNR_3R_4, in a protic solvent at ambient temperature;
- if R_4 is a (C_1-C_6) alkyl group, a compound of the formula R_4Li, in an anhydrous solvent at a temperature of between -20 and -80°C;
- if R_4 is a (C_1-C_6) alkyl group, a compound of the formula 1-alkenylcatecholborane, in the presence of a palladium catalyst, in an acetonitrile type solvent, at a temperature of between 50 and 80°C;
- if R_4 in the formula of the end product is a (C_1-C_6) alkyn-1-yle group, by reaction with a compound of the formula R_4H in the presence of copper iodide, palladium chloride, triphenylphosphine, and a base ;
- if R_4 in the formula of the end product is a (C_6-C_{12}) aryl group, by reaction with a compound of the formula $R_4B(OH)_2$, potassium phosphate and *tetrakis*-(triphenylphosphine)Pd(0), at a temperature of between 80 and 120°C, and preferably approximately 100°C;
- if R_4 in the formula of the end product is a OR_2 group, by reaction with an alcohol of the formula HOR_2 at ambient temperature;
- if R_4 in the formula of the end product is a SR_2 group, by reaction with a thiol of the formula R_4SH; or
- if R_4 in the formula of the end product is an SH group, by treating compounds wherein R_4 is an OH group with Lawesson's reagent.

21. A method of preparing of a compound of Formula (I) according to claim 1, wherein R_4 represents a chlorine atom, comprising reacting a compound of Formula (I') as defined in claim 1 with $POCl_3$.

22. A method of preparing of a compound of General Formula (I') according to claim 1, comprising the following steps:

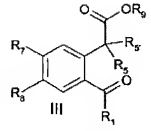
- reacting a compound of General Formula (II)



II

wherein R_5, R_5', R_7 and R_8 are as defined in claim 1 and R_9 represents a C_1-C_4 alkyl group, and preferably methyl, with a compound which comprises an acylating group of the formula R_1CO, to obtain a compound of Formula (III) wherein R_1, R_5, R_5', R_7 and R_8 are as defined in claim 1; and

- reacting the compound of Formula (III)



III

with hydrazine to obtain a compound of Formula (I') wherein R_1, R_5, R_5', R_7 and R_8 are as defined in claim 1.